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EXAMINER	
SHARAREH, SHAHNAM J	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/413,110	UNGER, EVAN C.	
	Examiner	Art Unit	
	Shahnam Sharareh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *116-131,138-141,146-151,160,164-166,168-174 and 178-184* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *116-131,138-141,146-151,160,164-166,168-174 and 178-184* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 06, 2005 has been entered.

Claims 116-131, 138-141, 146-151, 160, 164-166, 168-174, 178-184 are pending.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

2. Claims 116-131, 138-141, 146-151, 160, 164-166, 168-170, 173-174, 178-184 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siegel et al US Patent 5,695,460 in view of Porter US Patent 5,648,098.

3. Siegel discloses methods of utilizing an ultrasonic energy and an ultrasonic contrast agent containing perfluorinated microbubbles in combination with a thrombolytic agent to treat vascular thrombosis, (abstract; col 2 lines 1-65; examples 1-5; col 14, lines 4-30). Siegel specifically disclose that the ultrasound may be applied intravascularly by means of a miniature ultrasonic transducer or by a guide wire for transmitting ultrasound directly into the vessel (col 2, lines 7-10). Siegel's preferred ultrasound contrast agent is Echogen which contains phospholipids and polyethylene glycol (col 5, lines 50-53). Siegel et al further indicate the use of other types of contrast agents such as gas filled liposomes, or gas filled microbubble for their thrombus lysing method (col 5, lines 30-48). Siegel administers his drugs to an area in proximity of a thrombosis, which by its nature is hypoperfused..

Siegel describe applying ultrasonic energy to increase delivery of a bioactive agent from the vasculature through the vessel walls and into selected tissues, because the instant ultrasonic energy that produces cavitation or rupture of vesicles leading to increase delivery of bioactive agent from vasculature through the vessel walls are inherent to the process of Siegel. As the initial matter, the recitation of "increasing delivery of bioactive agents from the vasuclature" is viewed to be relative to an intravenous delivery process of a bioactive agent wherein no ultrasound energy is employed. Since Siegel employs at least some level of localized ultrasound energy, his

process is deemed to increase delivery of a bioactive agent, because it has shown that at least in the case of thrombosis, bioactive agents are more effective when used in conjunction with a gaseous contrast agent and external ultrasound energy. Thus, at least this limitation is inherent to the process of Siegel.

Second, the recitation of "delivery of bioactive agent from the vasculature through the vessel wall" is inherent to methods of intravenous delivery in general. Applicant appears to be ignoring the fundamentals of blood vessel anatomy, and the absorption of endogenous molecules through blood vessel structure. In order to assert their clinical benefits, bioactive agents administered intravenously must go through the vessel walls. In another words, absorption occurs through the vasuclature structure. It is well established in the art that blood vessels are composed of three cellular layers, and at least one of such layers, *Tunica Intima*, include endothelium cells that lines the lumen of all vessels. Such endothelium layer allows absorption of molecules through the vessel walls.[1] Therefore, such functional outcome is inherent to the process of administering drug intravenously. Subsequently, Siegel meets the limitations of the instant claims117-122, 129-131, 138-141, 160, 168-170, 173-174, 178-184

Finally, pages 67-70 and the examples 13 and 15 at pages 96-100 of the instant application describe the range of therapeutic ultrasound wherein cavitation and rupturing of microvesicles occur. More specially, at the bottom of page 68, the specification states:

> In therapeutic ultrasound, continuous wave ultrasound is used to deliver higher energy levels. For the rupture of vesicles, continuous wave ultrasound is preferred, although the sound energy may be pulsed also.

[1] See Absorption and distribution of Drugs, at pages 91-92 obtained from the website, ~~druglibrary.org/schaffer/ library/studies/ledain,~~ Last visited on June 10, 2004

> If pulsed sound energy is used, the sound will generally Preferably, the echo train lengths are about 20 pulses at a time. **In addition, the frequency of the sound used may vary from about 0.025 to about 100 megahertz (MHz).** In general, frequency for therapeutic ultrasound preferably ranges between about 0.75 and about 3 Mllz, with from about 1 and about 2 MHZ being more preferred. In addition, energy lè vels may vary from about 0.5 Watt (W) per square centimeter (cm2) to about 5.0 W/cmz, with energy levels of âom about 0.5 to about 2.5 W/cm2 being preferred. Energy levels for therapeutic ultrasound involving hyperthermia are generally from about 5 W/cm2 to about 50 W/cmz. For very small vesicles, for example, vesicles having a diameter of less than about 0.5 jtm, higher frequencies of sound are generally preferred. This is because smaller vesicles may be capable of absorbing sonic energy more effectively at higher âequencies of sound. When very high frequencies are used, for example, greater than about 10 MHz the sonic energy may penetrate fluids and tissues to a limited depth only. Thus, external application of the sonic energy may be suitable for skin and other superficial tissues.

In fact, the instant examples 13 and 15 respectively use 100 KHz and 200 KHz to cause cavitation of the microvessels. Since Siegel's energy waves falls within the 0.025-0.200 MHz range, it is also capable of providing therapeutic ultrasound within the meaning of the instantly claimed step (iii), the "cavitating and/or rupturing" step.

Siegel fails to explicitly teach the instantly recited ultrasound frequencies of "750 kHz to 3 MHz," or describe the suitable concentration of microvesicles for therapeutic purposes.

4. Porter specifically teaches desirable ultrasound energies that can be applied by conventional ultrasound devices. Such signals can vary from 20 kHz to several MHz and is generally applied in about 3 to 5 MHz. (see col 4, lines 47-50). Porter also teaches the effective use of perfluorocarbonated microbubbles alone at a rate of 0.0025-1ml/kg over about 1-25 minutes (which is roughly about 1.6×10^{-6} to 6×10^{-6} ml-kg/sec), wherein perfluorocarbon gas is perfluorobutane (see claims 1-5) and wherein the microbubble concentration was less than 0.8×10^{9} or greater than $1.5\ 10^{9}$ per each milliliter (col 6, line33-36). Thus, allowing an artisan to accurately measure the dose of the microbubbles during the infusion within the scope of the limitations of claims 146-151. Porter only fails to use vesicles containing phospholipids.

5. Nevertheless, absent a showing of unexpected results, it would have been obvious to one of ordinary skill in the art at the time of invention to optimize Siegel's ultrasound frequencies and the delivery rate by routine experimentation to achieve to a range between 750 kHz and 3 MHz.

One of ordinary skill in the art would have been motivated to do such modification, because as described by Porter, any conventional ultrasound diagnostic apparatus supplying an ultrasonic signal of 20 kHz to several MHz can be used to cause cavitation of microbubbles. Further, it is well established in the art that the key to induce an ultrasonic response in tissue and fluids lies in careful control of wavelength pulse duration, pulse energy and repetition rate of the ultrasound source. Thus, the ordinary artisan would have been motivated to optimize the frequency range of ultrasound waves for effective delivery of drugs at the site of interest.

6. Claims 116 –120, 160, 164-166, 171-174, 178-180 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlief US Patent 5,380,411 in view of Holmes et al (J. UROL. 144: 159-163, 1990).

7. Schlief teaches methods of destroying tumor tissues comprising intravenously administering to a patient a composition comprising gaseous microbubbles having a wall made of lecithin, polymers or combination and subjecting the patient to a filed of shock waves or ultrasound energy. (see col 1, line 35-col 2, line 67; col 5, lines 1-67, col 6, line 25-col 8, line 52). Schlief specifically states that for ultrasound irradiation, it is particularly advantageous to set the size of the microbubble so that their resonance frequency ies in the frequency range of the ultrasound. (col 1, lines 50-55). Accordingly,

such parameters as microbubble size and ultrasound frequency are viewed to be optimizable.

Schlief fails to specifically combine the therapy with a bioactive agent and apply ultrasonic energy at frequencies between 750KHz – 3 MHz.

8. Holmes et al show that focused high-energy shock waves in combination with a chemotherapeutic agent such as cisplatin or adriamycin delays the growth of solid tumors in prostate gland. (see abstract, also entire pages 159, 161-162).

9. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to combine the therapeutic modalities of Schlief with those of Holmes to improve the prognosis among patients in need of prostate tumor therapy, because it has been held prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus, claims that require no more than mixing together of two conventional compositions set forth prima facie obvious subject matter. *In re Kerkhoven*, 205 USPQ 1069. (CCPA 1980).

Further, as stated by Schlief optimizing such parameters frequency of ultrasound and microbubble size is well within purview of one of ordinary skill in the art. Thus, absent a showing of unexpected results merely modifying such parameters are not viewed to be patentable over the teachings of prior art.

Response to Arguments

10. Applicant's arguments filed May 06, 2005 have been fully considered but they are not persuasive.

11. Applicant argues that the instant methods are directed to cavitating or rupturing the vesicles at ultrasonic frequencies between about 750 kHz and 3 MHz. Applicant adds that Siegel's teachings are in direct contradiction of the instant claims. Applicant then concludes that there would have been not motivation to modify the Siegel reference towards the instant claims. (see arguments at page 10).

Again as argued throughout the prosecution, Examiner responds that Siegel's teachings are not a direct teaching away from the instant claims. Applicant appears to misinterpret what it means to "teach away" from a patented invention. Generally, "disclosed examples and preferred embodiments do not constitute a teaching which is away from a broader disclosure or nonpreferred embodiments." *In re Susi*, 169 USPQ 423 (CCPA 1971). "In general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the results sought by the applicant." *In re Gurley,* 31 USPQ2d 1130, 1131-2 (Fed. Cir. 1994).

In the instant case, the mere fact that there is an alternative means of improving drug delivery as described by Siegel does not preclude optimization of ultrasound frequencies or infusion rates that is obvious over Siegel in view of Porter.

Specifically, the portions of Siegel patents that Applicant characterizes as a "teaching away" (col 5, lines 29-31, 59-60) does not discourage one of ordinary skill in

the art to employ the frequencies instantly claimed. Siegel at col 5, lines 29-31 states that it has been found that when ultrasound is applied at a lower, rather than a higher frequency, the effectiveness of the method is markedly enhanced. The recitation of "higher frequencies" as used by Siegel does not teach against the instantly claimed ranges. In fact such recitation is relative and viewed to be open to optimization. One of ordinary skill in the art would have most likely performed further experimentation to determine what is the highest range of ultrasound frequencies capable of producing the same results described in Siegel.

Applicant adds that increasing frequencies in Siegels leads to a reduction of efficacy down to 26 % (see Arguments at page 10). First, such lines of arguments are not commensurate with the scope of the pending claims, as the instant claims are not directed to any degree of clot dissolution. Second, the instant claims are directed to enhanced delivery of drug relative to such delivery without the employment of ultrasound energy. Higher frequencies in Siegel, as argued by Applicant, still lead to a 25% improvement of clot dissolution, when compared to subjects not exposed to ultrasound energy. Thus, Siegle still shows an enhanced therapeutic response at its higher frequencies.

Finally, the element of motivation in an obviousness rejection considers the ordinary level of one of skilled in the art and not merely the teachings of one publication. Examiner concludes that a person of one ordinary skill reading the Siegel's reference would have been in possession of many teachings published prior to Siegel describing the use of ultrasound energy and various ultrasound emitting apparatus for enhancing

local drug delivery. One of such publications include Porter describing various ranges of ultrasound frequencies for drug delivery, as well as, Zohar US Patent 5,076,208 published in December of 1991, describing the use of ultrasound for administering drugs in an aquatic animals using a frequency of about 1MHz. Thus, the ordinary skill in the art would not have been discouraged from optimizing the path set out by Siegel, or would have taken a direction divergent from the path that was taken by the applicant. And, modifying the ultrasound frequencies or the rate of infusion would have been achieved by routine experimentation.

For reasons set forth above, Siegel does not "teach away" from the frequencies claimed here. In fact, Porter shows that the state of art does not discourage the use of instantly claimed ultrasound frequencies for drug delivery. (see col 4, lines 48-50). Thus, their combined teachings would have rendered the instant claims obvious, because one of ordinary skill in the art would have had a reasonable expectation to succeed in optimizing the rate of administration or ultrasound frequencies to improve availability of contrast agents and the end clinical outcome.

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 571-272-0630. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 571-272-0629. The

fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER